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Oral Ulcers as a presentation of secondary syphilis.

P. Thakrar [1], W. Aclimandos [2], D Goldmeier[3], J.F. Setterfield [1,4]

1.Department of Oral Medicine, Guy's & St Thomas' NHS Foundation Trust, London
2.Department of Ophthalmology, King's College Hospital, London
3.of Genitourinary medicine, Imperial College NHS Healthcare Trust, London.
4.Mucosal and Salivary Biology, Dental Institute, King's College, London

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Corresponding Author:
Dr Jane Setterfield, Consultant Dermatologist, Department of Oral Medicine, Guy's and St.Thomas' Hospital, Great Maze Pond, London SE1 9RT.
02071884399. Jane.setterfield@kcl.ac.uk

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P. Thakrar, [1] W. Aclimandos, [2] D Goldmeier[3] and J. F. Setterfield[1,4]

[1]Department of Oral Medicine, Guy's & St Thomas' NHS Foundation Trust, London, UK; [2]Department of Ophthalmology, King's College Hospital, London, UK; [3]Department of Genitourinary medicine, Imperial College NHS Healthcare Trust, London, UK; and [4]Mucosal and Salivary Biology, Dental Institute, King's College, London, UK

Abstract

The incidence of syphilis is increasing and typically presents in patients with known risk factors, often to genitourinary physicians. Cases presenting to a dermatologist or ophthalmologist will more likely have secondary syphilis, which is potentially associated with complications. Early recognition is therefore vital to limit both the disease and risk of further contact spread. In this review, we include two case histories demonstrating the value of recognizing oral signs. Additionallym we review the currently accepted diagnostic and therapeutic recommendations.

Introduction

Syphilis is a systemic bacterial infection caused by the spirochaete *Treponema pallidum*, and was first reported in Italy at the end of the fifteenth century.[1] There was a major syphilis epidemic in the 1940s, associated with wartime, and this was followed by a decline at the start of the antibiotic era. However, recently there has been an increase in the number of cases reported in western populations particularly among men having sex with men (MSM).[2, 3]

The clinical presentation of both early and late syphilis is diverse, meaning that diagnosis can often be delayed or even missed. Syphilis is transmitted by direct contact with an infectious lesion, almost always sexual, or by transplacental passage through pregnancy. In heterosexual patients, bacterial entry is typically genital or oral, but in MSM, it may often be extragenital (anal, rectal, oral).[4] From the primary stage onwards, bacteria disseminate via the blood and lymphatics. Public Health England (PHE) has reported a 12% increase in syphilis between 2015 and 2016 and an overall 97%increase since 2012, mainly in MSM.[5]

The 2015 Syphilis guidelines from the British Association for Sexual Health and HIV, term the primary, secondary and early latent phases (in the first 2 years of infection) of syphilis as early-stage syphilis, and usually late latent or less commonly tertiary syphilis as late-stage syphilis. The primary stage is highly infectious, with a chancre affecting typically the glans penis/vulva or the lips and tongue. Up to 40% of patients at this stage can go undiagnosed,[6] and his stage may well pass unnoticed by the patient. Without treatment, the lesion heals within 3–8 weeks but the bacterial infection may progress, and secondary syphilis will appear in 25% of patients.[4,7,8] Secondary syphilis is a systemic disease and therefore may present to various specialities.

Clinicians must keep syphilis in their list of differential diagnoses. However, in up to 15% of patients, the initial VDRL (nontreponemal test) screening test may be negative, thus the diagnosis may be missed. Most UK laboratories now screen with a treponemal test. Table 1 highlight two diagnostically challenging cases that were referred to Dermatology after being seen by various other medical specialities. Both cases presented with oral ulceration as their primary symptom, but careful history-taking and other features raised suspicion of possible secondary syphilis.

Clinical features

Oropharyngeal lesions are not unusual in secondary syphilis but in the absence of known risk factors, as in our two immunocompetent patients, it may be overlooked.[9] The differential diagnosis of patients presenting with atypical persistent oral ulceration must therefore include syphilis, and Table 2 shows possible differential diagnoses.

Oral manifestations may include ulceration or pseudomembranous lesions such as mucous patches, keratoses, plaques or less commonly gummata. The palmar/plantar skin can simultaneously demonstrate an eruption of symmetrical coppery maculopapules.[10] Nodular skin lesions may also occur, and are seen typically on the face, limbs and back. Patients may also report fever, malaise, myalgia and weight loss, with a range of nonspecific symptoms. Systemic complications of syphilis must additionally be considered, as sequelae may be lasting and serious. Transient hepatitis with only mildly raised alkaline phosphatase, and rarely glomerulonephritis or splenomegaly can also occur as a result of secondary syphilis. In Patient 1 (Table 1), the history of hepatitis, although transient, was likely to have been associated with secondary syphilis. Adachi *et al*. showed that 39% of their patients had liver abnormalities in early-stage syphilis.[11]

In Patient 2 (Table 1) the presumptive diagnosis of ocular sarcoid was made on the basis of pan-uveitis and elevated serum angiotensin-converting enzyme. However, both can be present in secondary syphilis and must be considered in the wider clinical context. Ocular neurosyphilis is a rare manifestation but can present as early (meningovascular as part of secondary syphilis) or late-stage infection (tabes, general paresis or meningovascular as part of tertiary) and carries a risk of permanent blindness. It is estimated that 1.1% of uveitis cases are due to syphilis. [12] Other ocular signs may include optic neuropathy, interstitial keratitis and retinal involvement.[13] In addition, 1–2% of patients with secondary syphilis may have neurological symptoms such as acute meningitis and cranial nerve palsies. All patients with neurological symptoms in suspected or confirmed syphilis should undergo a full neurological examination.[4]

Patients with human immunodeficiency virus (HIV) may present with more atypical syphilis and progress to secondary syphilis without early detection. Owing to co-infection with HIV, the clinical picture may mimic that of opportunistic infections.[14] Other differences may include a more severe secondary syphilis with earlier neurological involvement[15]Of particular note, ocular disease may be the presenting sign in those with syphilis and co-infection with HIV.[16,17] Therefore, patients should be counselled and tested for HIV if status is not already known. Early detection is vital, as the severity of ocular disease has also been shown to be higher when HIV co-infection is present. [18] Interestingly Patient 2, an HIV-negative man, presented with ocular syphilis.

Diagnosis

The diagnosis of syphilis is based on a full sexual history, clinical examination, serological tests and histopathological examination.[6] Indirect laboratory tests of serum or cerebrospinal fluid are still the most routinely used. Syphilis can be missed if appropriate serological tests are not undertaken at the outset. *T. pallidum* can infect any organ and produce a clinical disease with a relapsing and remitting course, therefore making diagnosis difficult in those deemed at low risk.

In primary syphilis, VDRL is positive in up to 75% of cases, but as in our first patient, there may be false negatives. This can also occur in secondary or late disease and is termed the prozone phenomenon.[10,19] Syphilis serology should include both nontreponemal test (NTT) and *Treponem*a test (TT). Traditional syphilis algorithms use NTT followed by TT, whereas more recent accepted algorithms utilize TT including enzyme immunoassay as first-line testing. Positive samples then undergo quantitative NTT[4,20, 21] (Table 3).

Treatment

Treatment of syphilis is dependent upon the stage of disease (Table 4). In early syphilis in the immunocompetent patient, treatment is most effective via the parenteral route (single-dose benzathine penicillin 2.4 MU) as it ensures bioavailability and a continuous serum treponemacidal antibiotic level for at least 7 days.[22] However, it is unlicensed in the UK and therefore needs to be discussed and documented with the patient prior to treatment.[4] In patients allergic to penicillin, or, where a nonintramuscular route is preferred, a second-line agent such as doxycycline should be used. Treatment response is measured both clinically and serologically, with the aim of achieving a reduction of four-fold or greater in rapid plasma reagin titre. Patients with ocular involvement should be managed via the neurosyphilis pathway,[4,12,23] including a full neurological assessment, consideration of baseline brain computed tomography/magnetic resonance imaging scan, lumbar puncture and higher doses of treatment (Table 4).

Conclusion

The two cases presented here highlight the need to consider syphilis early on in patients presenting with atypical oral lesions/ulceration.[24] Both cases presented with persistent relatively painless oral ulceration. Biopsy of unsuspected lesions often requires special stains.[25] Leuci *et al*. reviewed the oral manifestations of syphilis in primary, secondary and tertiary stages, and found them to be present in 17%, 58% and 25% of cases respectively. Clinical phenotypes ranged from typical chancres in the primary stage through to mucous patches, keratosis, mucosistis and chancres in the secondary and tertiary stages.[26] In summary, early diagnosis and treatment of syphilis is paramount to prevent further contact spread and disease complications.

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Learning points

- The incidence of syphilis is increasing and clinicians should recognize the varied presentation.
- A sexual history is essential.
- Where there is clinical suspicion, immunohistochemical stains are very helpful in histopathological examination of oral tissues but *Treponema*-specific serology is essential.
- Cases presenting to Dermatology are more likely to be secondary and thus may be associated with serious long-term complications.
- Within the UK, benzathine penicillin is often difficult to obtain, and second-line doxycycline is most commonly used.

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Figure 1 Patient 1 had extensive mucous patches with a yellow–grey base in ulcerated areas and a serpiginous edge seen at the commissure of the lips. The ulcers were soft to palpation and demonstrated raised margins.

Figure 2 (a,b) Patient 1. (a)Low power view showing discontinuous mucosal epithelium covered by fibrinous exudate containing a dense neutrophil infiltrate. The subepithelial infiltrate consists mostly of plasma cells."

(b)Higher power view showing fibrin above ulcerated epithelium with a dense neutrophil infiltrate." Haematoxylin and eosin, original magnification (a) × 40; (b) × 160 (c,d) *Treponema pallidum* rabbit polyclonal antibody immunostaining showing (c) prominent staining in corium within an area of ulceration and (d) multiple spirochaetes. Original magnification (c) × 80; (d) × 320.

Figure 3 (a–c) Symmetrical ulceration on soft palate with subtle raised margins; (b) normal right fundus; (c) focal retinal pigment epithelial changes and a retinal vein occlusion typical of syphilitic chorioretinitis in the left fundus.

Table 1 Case reports of a patient presenting with persistent oral ulceration, and a second referred by the ear, nose and throat department for oropharyngeal ulceration.

	Patient 1	Patient 2
Presentation	45-year-old Arab man with a 2-month history of persistent oral, genital and facial skin lesions.	50-year-old Australian man with a 3-month history of a persistent sore throat despite oral antibiotics and fluconazole
History	Inpatient stay in Kuwait for 3 months with unexplained hepatitis. Had seen a number of dermatologists and a sexual health clinic regarding his oral ulcers. Serological tests for HIV, VDRL were negative. HSV1/2 tests were positive	Had seen an ophthalmologist and ENT surgeon
Previous treatment	Aciclovir 800mg 5× a day for 4 weeks	Prednisolone and short courses of antibiotics

Medical history	Type 2 diabetes, coronary artery bypass graft. Medications: metformin, sitagliptin, glimepiride, bisoprolol, indapamide, aspirin, candesartan and rosuvastatin, none of which had coincided with the onset of his oral ulceration	Recent diagnosis of ocular sarcoidosis based on an initial presentation of panuveitis and a raised serum angiotensin-converting enzyme level. Had presented with left anterior uveitis that responded well to topical steroids. but a few days later, his ocular disease progressed to a marked vitritis with unilateral visual impairment. He had responded poorly to oral prednisolone.
Sexual history	Married with two children	MSM. Recent HIV testing was negative
Clinical findings	No significant cervical or inguinal lymphadenopathy (see Fig. 1)	Oral manifestations (Fig. 3). No palpable cervical or generalized lymphadenopathy but had a generalized maculopapular rash
Investigations	Blood tests including syphilis serology. Mucosal biopsies for histology and direct immunofluorescence	Blood tests including syphilis serology
Results	Raised white cell count 16×10^9/L, elevated serum IgG 19.76 g/L (7–16 g/L). Positive HSV type 1 and 2 IgG serology and negative HIV serology. RPR (titre 1 : 64) and TPHA-positive, confirming a treponemal infection	RPR (1 : 128) and TPPA confirmed a treponemal infection
Results: Histology	Initial histopathology report inconclusive and PAS stains negative for fungi (Fig. 2a,b). Subsequent immunostaining with rabbit polyclonal antibody to TPRPA revealed numerous microorganisms (Fig. 2c) identified as spirochaetes (Fig. 2d).	–
Treatment	Benzathine penicillin was not available and treatment with doxycycline 100 mg twice daily for 14 days was given, resulting in rapid healing of the oral and genital lesions. Patient returned to his home country for further management and follow-up	Reassessed by Ophthalmology at request of Dermatology; diagnosis of ocular neurosyphilis was confirmed and as the left vitritis cleared the patient was noted to have retinal pigmented epithelial lesions and a retinal vein occlusion typical of syphilitic uveitis (Fig. 4a,b). Patient was allergic to penicillin therefore was commenced on doxycycline 200 mg twice daily for 28 days while continuing on prednisolone. His corrected left visual acuity improved from 6/36 to 6/9

ENT, ear, nose and throat; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MSM, men who have sex with men; PAS, periodic-acid–Schiff; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* haemagglutination test; TPPA, *Treponema pallidum* particle agglutination assay; TPRPA, Treponema pallidum rabbit polyclonal antibody; VDRL, Venereal Disease Research Laboratory.

Table 2 Differential diagnosis of oral mucosal lesions in suspected syphilis.

Atypical aphthae
Bacterial infection such as syphilis
Fungal infection such as paracoccidiomycosis
Granulomatous inflammation

5. Autoimmune: pemphigus/pemphigoid
Squamous cell carcinoma
Traumatic ulceration
Drug-related manifestation
Bullous or ulcerative lichen planus

Table 3 Summary of serological tests used for syphilis

NTT; measure antibody response in relation to cardiolipin release from damaged host cells	VDRL	Measures IgG and IgM antibodies. Primary use is in testing CSF fluid. If positive, then a positive TT test is required to confirm diagnosis. False negatives can happen due to prozone. May be negative in late syphilis
	RPR	Measures IgG and IgM antibodies. Used on serum samples. Useful in monitoring treatment of syphilis. False negatives can happen due to prozone. May be negative in late syphilis
TT: assays can detect either IgM or IgG antibodies. Act as confirmatory test when NTT is positive. Use *T. pallidum* or its components as the antigen	EIA (based on recomnbinant treponemal antigens) TPHA TPPA FTA-ABS	Uses serum samples. Can be used as screening or confirmation tests. A positive result can represent previously treated or untreated syphilis. If one of these tests is positive, should be followed up with a different TT and this in turn should be followed by NTT.

CSF, cerebrospinal fluid; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; NTT, nontreponemal test; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* haemagglutination test; TPPA, *Treponema pallidum* particle agglutination assay; TPRPA, Treponema pallidum rabbit polyclonal antibody; VDRL, Venereal Disease Research Laboratory; TT, *Treponema* test.

Table 4 Overview of treatment recommendations: adapted from the UK national Guidelines on Syphilis 2015.[4]

Stage of syphilis	Treatment	Comments
Early(primary/secondary)	Benzathine penicillin 2.4 MU IM single dose OR procaine penicillin G 0.6 MU IM daily 10 days. Doxycycline 100 mg PO BD 14 days. Ceftriaxone 500 mg IM daily 10 days. Amoxycillin 500 mg PO QDS plus probenecid 500 mg 14 days	NB: doxycycline supersedes all other tetracyclines. Macrolide therapy should be used as a last resort. Treatment of HIV-negative and HIV-positive patients should follow the same regimen
Latent (gummatous syphilis and CVS involvement)	Benzathine penicillin 2.4 MU IM weekly for 3 weeks (three doses) OR procaine penicillin 0.6 MU IM OD for 14 days Doxycycline 100 mg PO BD for 28 days Amoxicillin 2 g PO TDS plus probenecid 500 mg QDS for 28 days	—

Neurosyphilis	Procaine penicillin 1.8-2.4 MU IM OD plus probenecid 500 mg PO QDS for 14 days OR doxycycline 200 mg PO BD for 28 days. Amoxicillin 2 g PO TDS plus probenecid 500 mg PO QDS for 28 days Ceftriaxone 2 g IM or IV OD for 10–14 days	Steroids should be given with all antitreponemal antibiotics for cardiovascular and neurological syphilis; 40–60 mg prednisolone OD for 3 days, starting 24 h before the antibiotics

BD, twice daily; CVS; cardiovascular system; ENT, ear, nose and throat; HIV, human immunodeficiency virus; PO, per os; IM, intramuscular, IV, intravenous; QDS, four times daily; TDS, three times daily.

CPD questions

Learning objective

To demonstrate up-to-date knowledge on syphilis and its management.

Question 1

What is the recommended treatment for early syphilis in patients who are allergic to penicillin?
(a) Ceftriaxone 1000 mg intramuscularly daily for 10 days.
(b) Doxycycline 100 mg orally twice daily for 14 days.
(c) Doxycycline 200 mg orally twice daily for 28 days.
(d) Doxycycline 150 mg orally three times daily for 14 days.
(e) Cephalexin 250 mg orally four times daily for 14 days.

Question 2

Which nontreponemal test should be used on cerebrospinal fluid (CSF)?
(a) Rapid plasma reagin (RPR).
(b) *Treponema pallidum* particle agglutination assay (TPPA).
(c) Fluorescent treponemal antibody absorption assay (FTA-ABS).
(d) Venereal Disease Research Laboratory (VDRL).
(e) Enzyme immunoassay (EIA).

Question 3

Which clinical sign is commonly associated with late/tertiary-stage syphilis?
(a) Chancre.
(b) Gummata.
(c) Snail-track ulcer.
(d) Blepharitis.
(e) Rash.

Question 4

Within current practice, which test should be requested first on suspicion of syphilis?
(a) Nontreponemal test.
(b) Treponemal test.
(c) Lumbar puncture.
(d) Magnetic resonance imaging (MRI) of the brain.
(e) Dark-field microscopy.

Question 5.

Which drug should be considered in neurosyphilis before giving penicillin? Usually given 24–48 h before

the antibiotic..
(a) Probenecid.
(b) Prednisolone.
(c) Hydrocortisone.
(d) Chlorphenamine.
(e) Aciclovir.

Question 1

What is the recommended treatment for early syphilis in patients who are allergic to penicillin?
(a) Incorrect. Ceftriaxone is given at 500 mg intramuscularly, not 1000 mg.
(b) Correct. Doxycycline 100 mg PO BD should be given in those that are allergic to penicillin for 14 days.
(c) Incorrect. The dose of doxycycline is 200 mg only in neurosyphilis.
(d) Incorrect. Doxycycline is never given at a dose of 150 mg for treatment of syphilis.
(e) Incorrect. Cephalexin is not a recommended antibiotic therapy for syphilis.

Answer 2

Which nontreponemal test should be used on cerebrospinal fluid (CSF)?
(a) Incorrect. RPR is not recommended on CSF.
(b) Incorrect. TPPA is a treponemal test.
(c) Incorrect. FTA-ABS is a treponemal test.
(d) Correct. VDRL can be used on CSF.
(e) Incorrect. EIA is a treponemal test.

Answer 3

Which clinical sign is commonly associated with late/tertiary-stage syphilis?
(a) Incorrect. Chancre is usually seen at the initial site of exposure.
(b) Correct. Gummata are classic late-stage clinical signs.
(c) Incorrect. Snail-track ulcers are usually seen in early-stage disease.
(d) Incorrect. Blepharitis is not associated with syphilis.
(e) Incorrect. Rash is seen in early-stage disease.

Answer 4

Within current practice, which test should be requested first on suspicion of syphilis?
(a) Incorrect.
(b) Correct .
(c) Incorrect. Lumbar puncture has been used in management of neurosyphilis but is not a first-line investigation.
(d) Incorrect. MRI of the brain scan is not a first-line investigation.
(e) Incorrect. Dark-field microscopy is used on pathology samples.

Answer 5

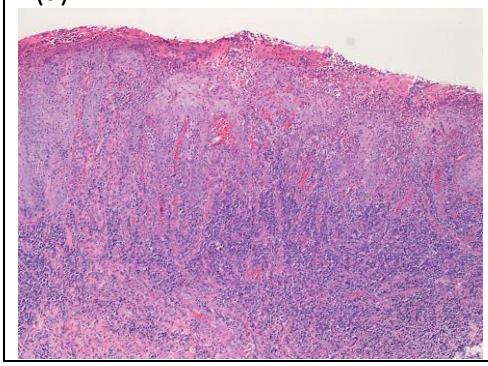
Which drug should be considered in neurosyphilis before giving penicillin? Usually given 24–48 h before the antibiotic.
(a) Incorrect. Probenecid is given along with amoxicillin.
(b) Correct. Prednisolone should be given 24 h prior to the antibiotic.
(c) Incorrect. Hydrocortisone is not given. Prednisolone is the preferred drug.
(d) Incorrect. Chlorphenamine is not used in treating syphilis.
(e) Incorrect. Aciclovir, being an antiviral drug, is not indicated.

FIGURES

Figure 1

Figure 2:

2(a)



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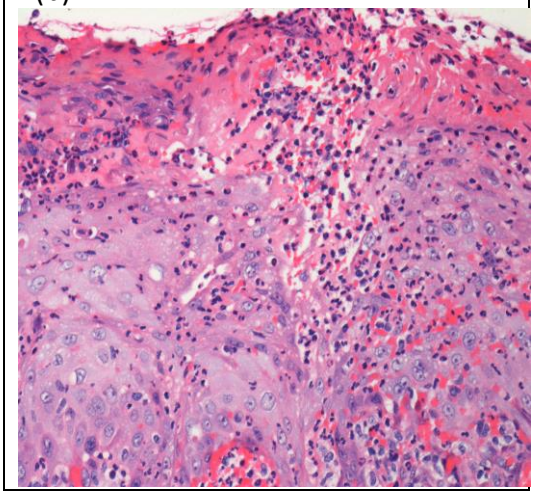

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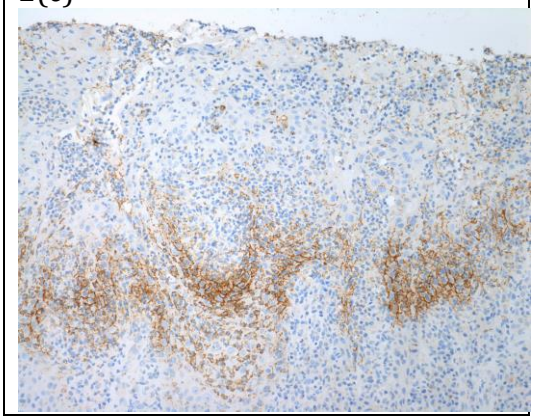

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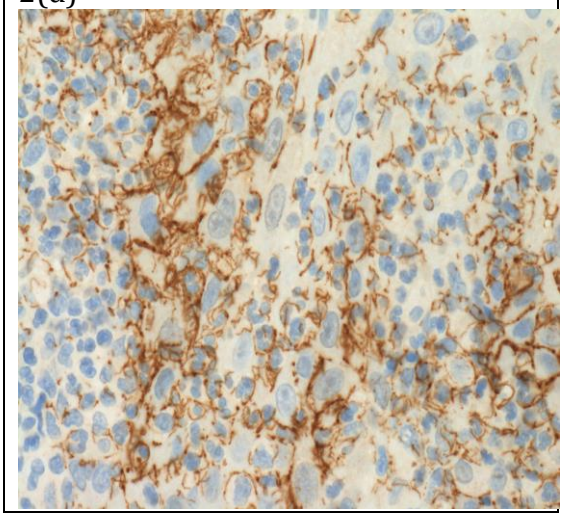

Figure 3

Figure 4:

4(a)

4(b)